



Editorial

Asthma, Chronic Obstructive Pulmonary Disease and Other Combinations[☆]



Asma, enfermedad pulmonar obstructiva crónica y otros combinados

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The delicious combination of gin and tonic (carbonated water with quinine) not only helped prevent malaria, it also helped to consolidate the British Empire. And, quite unexpectedly, it has stimulated scientific reflection among the authors of this editorial, prompting us to propose a translational research strategy that might be a precursor of a “from bar to bedside” approach, as we have extracted analogies from real life that may later be carried over to clinical practice. With a little imagination, we can see gin as a phenotype of the alcoholic drinks endotype, and tonic as a phenotype of the soft drinks endotype. It would be just as absurd to categorize gin and tonic as phenotype of gin or a phenotype of tonic, as it would be to suggest that the asthma-COPD overlap syndrome (ACOS) is a phenotype of either of these 2 diseases. That both diseases happen to occur in the airway should result in a process that combines the inflammatory characteristics of each, in the same way as the mixing of gin and tonic in the same glass preserves the properties of each of the 2 drinks, but produces another entirely different tippel. In general, the gin is put in before the tonic, just like asthma generally precedes COPD, but pouring the mixer in the glass before the alcohol (it is rare for COPD to present first) will not change the end product.

For this hypothesis to be true, certain premises must be met: Patients with ACOS have a mixed inflammatory pattern, with elements pertaining to both COPD (Th1) and asthma (Th2). This mixed inflammatory pattern has clinical and prognostic characteristics that are different from those of asthma and COPD when they present separately. Taken together, the foregoing premises result in a different therapeutic approach to that used in COPD or asthma.

If these premises are met, ACOS could be classified as a syndrome, but until this is proven, some authors recommend dropping the S from the acronym and suggest that ACO would merely be the result of these 2 diseases coinciding in the same individual.¹ What

does seem clear is that the great majority of specialists (84% in Spain) recognize ACOS as, at least, a clinical reality.²

What is the Proof of all this?

Kitaguchi et al., in a small retrospective study, observed that patients with COPD and asthma symptoms had higher eosinophil levels in blood and sputum,³ but studies involving larger populations of chronic obstructive airway disease (COAD) patients, including ACOS, COPD and asthma cases, are required to establish characteristic inflammatory patterns (if they exist) and to determine the stability of such patterns over time.

Some controversy exists with regard to the clinical and prognostic impact of ACOS. One study⁴ concluded that exacerbations are more frequent and severe and that quality of life is poorer in ACOS, while others⁵ found the opposite. These differences can be explained by how the syndrome is defined in each publication, or by the varying severity of the populations studied. It could be conjectured that, in patients with ACOS and mild obstruction, the burden of asthma could be heavier than that of COPD, which would result in a better therapeutic response and more favorable prognosis. In patients with severe obstruction, however, COPD would predominate, the margin for improvement would be reduced and the concomitant asthma would further aggravate symptoms and exacerbations.

Obviously, incomplete understanding of the pathophysiology of ACOS and uncertainties regarding the prognosis and distinctive clinical characteristics of the condition make it impossible to define evidence-based therapeutic strategies, although it is safe to assume that treatments that are effective for COPD and asthma will also be effective for ACOS.

What are the Problems of Investigating Asthma-COPD Overlap Syndrome in the Clinic?

Most of the studies performed to date to determine the prevalence and characteristics of ACOS have been misdirected, since exclusively COPD populations have been selected.^{4,5} Studies should focus on a COAD population, and the clinical and disease

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characteristics that identify each of the variants, whether asthma, COPD or ACOS, need to be investigated. This was partially achieved by Van Boven et al.⁶ in a retrospective cohort of patients with asthma and COPD. They found that patients with both diagnoses were more frequently women, they were younger, with a greater prevalence of rhinitis, anxiety, gastroesophageal reflux, and osteoporosis than patients classified as having COPD only. In contrast, COPD-only patients had higher rates of ischemic heart disease and renal failure than patients with both asthma and COPD.

It should be pointed out that a potential drawback of this type of study will be the lack of a clear definition of ACOS. Focusing on symptoms or lung function (non-specific) will make it difficult to differentiate ACOS from asthma and COPD. If we decide to use biomarkers which reflect underlying inflammation to a greater or lesser extent (eosinophilia in sputum or blood, periostin, FENO, etc.), patients will be grouped according to their biomarker levels, and each resulting category will include patients with COPD, asthma, or both. Implementing this strategy involves accepting that biomarkers are not fully validated, they are inaccurate for identifying clinical phenotypes (e.g., not all early-onset allergic asthmas show eosinophilia), and they vary widely in the same individual over time, either spontaneously or as a result of treatment.

Whatever the method chosen to categorize patients with COAD (symptoms and function or biomarkers), we will find that the clinical and prognostic differences among the different groups may be as much due to underlying pathophysiology as to the grade of severity produced by the level of bronchial obstruction, thus confounding any attempt to reach conclusions.

How Can We Unravel the Problem and Celebrate with a Gin and Tonic?

Since the times of the Ciba Guest Symposium in 1959, COPD has been conceived as an overlap between chronic bronchitis, emphysema and asthma subtypes associated with bronchial obstruction,⁷ a notion first represented in a non-proportional Venn diagram by Snider.⁸ According to the Dutch hypothesis,⁹ asthma, chronic bronchitis and emphysema could be considered different

expressions of COAD. There would a genetic predisposition to presenting COAD, and exposure to environmental factors (allergens, tobacco, infections, irritants, etc.) would determine whether the disease manifests in one or other obstructive process. However, studies performed to identify a common genetic component have been unsuccessful.¹⁰

Definitively, it seems more reasonable to study how inflammatory markers correlate with different clinical characteristics and prognoses, and to examine the overall population of COAD patients and their wide spectrum of severity. Ideally, studies should be longitudinal to confirm the stability of the classification over time. This is the only way to establish if ACOS is a different clinical entity from its 2 component parts. We hope that the SEPAR initiative, the CHACOS study, will help resolve some of these issues.

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